PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	02.07.2004
Applicant's or agent's file reference: RLL-261WO	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB 03/02696	08.07.2003	08.07.2002

Applicant
RANBAXY LABORATORIES LIMITED

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Ambroa, J.R. Tel. +49 89 2399-8012

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference RLL-261WO	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/IB 03/02696	International filing date *(day/month/year)* 08.07.2003	Priority date *(day/month/year)* 08.07.2002
International Patent Classification (IPC) or both national classification and IPC C07D207/34		
Applicant RANBAXY LABORATORIES LIMITED		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
06.02.2004	02.07.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Fanni, S Telephone No. +49 89 2399-8712

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IB 03/02696

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-14 as originally filed

Claims, Numbers

1-66 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 65-66

   because:

   ☒ the said international application, or the said claims Nos. 65-66 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees, the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☒ all parts.

☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1,48
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1, 48
Industrial applicability (IA)	Yes:	Claims	1,48
	No:	Claims	

2. Citations and explanations

see separate sheet

ITEM III

Claims 65 and 66 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT). See also the paragraph on : "Industrial applicability" in item V below.

ITEM IV

The present application is directed to 3-carbamoyl pyrroles of formula I according to present claim 1 which are useful as hypocholesteromic agent, due to inhibition of HMG-CoA reductase. For purposes of unity of invention, Rule 13.1 PCT stipulates that an international application must relate to one invention only or to a group of inventions so linked as to form a single general (inventive) concept.

3-carbamoyl pyrroles as inhibitors of HMG-CoA reductase are also disclosed in US 5385929 (D1) and US5298627 (D2). The subject matter of D2 interferes with the Markush formula according to present claim 1, although no specific examples from the said document fall within the scope of present claim 1.

In view of the said prior art, the problem to be solved by the present application may have been the provision of further compounds having the same activity and utility.

Compared with the prior art, divergent solutions to this problem could be defined as subject-matter of the claims of the present application, based on different substituent patterns of the 3-carbamoyl substituent known from the prior art. This could for example mean that the following different approaches (problems) would have been considered by the person skilled in the art:

a) compound of formula I according to present claim 1 where both R4 and R5 are hydrogen;

b) compound of formula I according to present claim 1 where both R4 and R5 are C1-C6 alkyl or one of R4, R5 is C1-C6 alkyl and the other is hydrogen;

c) compound of formula I according to present claim 1 where both R4 and R5 are C1-C3 cycloalkyl or one of R4, R5 is C1-C3 cycloalkyl and the other is hydrogen;

d) compound of formula I according to present claim 1 where both R4 and R5 are optionally substituted benzyl as defined in present claim 1 or one of R4, R5 is optionally substituted benzyl as defined in present claim 1 and the other is hydrogen;

e) compound of formula I according to present claim 1 where both R4 and R5 are substituted phenyl as defined in present claim 1 or one of R4, R5 is substituted phenyl as defined in present claim 1 and the other is hydrogen;

The only element in common between the above four groups of inventions is represented by the core 3-carbamoyl pyrrole moiety. This cannot, however, be considered - within the meaning or Rule 13.1 PCT - as a special technical feature linking the above four groups of subject-matters, since the use of 3-carbamoyl pyrroles as inhibitors of HMG-CoA reductase is known from the prior art.

Thus, no technical link can be seen between the above five groups of inventions. Consequently there is a lack of unity within the meaning of Rule 13 PCT.

ITEM V

NOVELTY 33(2) PCT

The present subject matter differs from D1 mainly on account of the present proviso that if only one of R6-R10 is hydroxy or protected hydroxy, at least on of the others R6-R10 is not hydrogen.

The present subject matter overlaps with D2 of which if could be considered a novel selection on account of the the carbamoyl residue ever present at position 3 of the present pyrrole ring.

INVENTIVE STEP (Article 33(3) PCT)

The present subject matter discloses 3-carbamoyl pyrroles which are inhibitors of HMG-CoA reductase.

For present groups of inventions a-d, D2 is considered to be the closest prior art and

discloses 3-carbamoyl pyrroles which are inhibitors of HMG-CoA reductase.

The subject matter of present groups of inventions a-b overlaps with D2, although no specific examples of D2 falls within the scope of present claims. The subject matter of present group of inventions c) differs from D2 on account of the fact that at least one of R4 or R5 is cycloalkyl. However, it appears that the equivalence between cycloalkyl and alkyl is disclosed in D2 (cf definition of R2 and R3). The subject matter of the present group of inventions d) differs from D2 on account of the fact that at least one of R4 or R5 is a benzyl derivative. This appears however to be a minor modification in the periphery of the core structure disclosed by D2. Thus, the problem to be solved by the subject matter covered by group of invention a-d is considered to be the provision of 3-carbamoyl pyrroles which have unexpected properties when compared to the closest prior art compounds from D2, i.e. unexpectedly solve a problem not yet solved by D2. In the absence of any evidence that the compounds of each of the present groups of inventions a-d have indeed unexpected properties when compared to the closest prior art compounds, an inventive step cannot be acknowledged for any of the present group of inventions a-d.

For present group of invention e), D1 is considered to be the closest prior art and discloses 3-(hydroxyphenyl)carbamoyl pyrroles which are inhibitors of HMG-CoA reductase. The subject matter of e) differs from D1 on account of the second proviso of present claim 1, for which at least one of the present R6-R10 substituent must be (protected) hydroxy and at least one of the other is not hydrogen. Thus, the subject matter of present group of inventions e) is obtainable by adding a further substituent at the periphery of a core structure which is known from D1 to have the desired activity. The problem to be solved by the present subject matter is therefore considered to be the provision of 3-(hydroxyphenyl)carbamoyl pyrroles which have unexpected properties when compared to the closest prior art compounds from D1, i.e. unexpectedly solve a problem not yet solved by D1. However, a comparison between present compounds according to group of invention e) and compounds according to D1 does not appear to be found in the present application, and the reported comparison with Atorvastatin is not suitable for the purpose of establishing an inventive step over D1, the compound according to D1 having already been shown to be more active than Atorvastatin. Thus, in the absence of any evidence that the present compounds have indeed unexpected properties when compared to the closest prior art compounds, an inventive step cannot be acknowledged for present group of inventions e).

INDUSTRIAL APPLICABILITY (Article 33(4) PCT)

For the assessment of the present claims 65-66 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.